Solution

111-1060

Patent
Attorney's Docket No. 010095-003e

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

#8



In re Patent of )
)
Braham Shroot, et al )
)
U.S. Patent No.: 5,212,303 ) Attn: Box Patent Extension
)
Issued: May 18, 1993 )
)
For: BENZONAPHTHALENE )
DERIVATIVES, A PROCESS FOR )
THEIR PREPARATION AND THEIR )
USE IN THERAPEUTIC AND )
COSMETIC COMPOSITIONS )



**APPLICATION FOR EXTENSION OF PATENT TERM**

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

This application is submitted by including an original, a certified copy and three working copies.

Under the provisions of 35 U.S.C. §156 and in accordance with 37 C.F.R. §1.710 *et. seq.*, the owner of record of U.S. Patent No. 5,212,303 ("the '303 Patent"), requests that the term of the '303 Patent be extended 13 days to expire on May 31, 2010. The '303 Patent issued May 18, 1993, and would in view of GATT, and in the absence of an extended term, expire on May 18, 2010. The named inventors are Braham Shroot, Jacques Eastache and Jean-Michel Bernardos. The patent is assigned of record to Centre



International de Recherches Dermatologiques ("CIRD"), Valbonne, France. The patent is

licensed to Galderma Laboratories, Inc., who was the marketing applicant for the NDA for DIFFERIN Solution, 0.1%. As background, Centre International de Recherches Dermatologiques (CIRD) and Galderma Laboratories, Inc. are both organizations existing under the joint ownership of Nestlé S.A. and L'Oréal.

The items required by 37 C.F.R. §1.740(a) follow in §§ I-XVII.

## I. APPROVED PRODUCT

The approved product, having the tradename "DIFFERIN Solution, 0.1%", is a solution containing adapalene. Each milliliter (ml) of DIFFERIN Solution contains adapalene 0.1% (1 mg), in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v). Specifically, DIFFERIN contains, per g, the following ingredients:

| Ingredient | per g | percent (w/w%) |
|---|---|---|
| adapalene | 1 mg | 0.10% |
| polyethylene glycol 400. NF | 0.699 g | 69.9% |
| SD alcohol 40-B, anhydrous | QS to 1 g | QS to 100.0% |

The finished dosage form of DIFFERIN has a specific gravity of 1.003-1.009. Since DIFFERIN Solution is in the form of a liquid, the concentrations of adapalene and alcohol will be expressed in the form of weight-to-volume measures for labeling purposes.

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. The molecular formula is $C_{28}H_{28}O_3$ and the molecular weight is 412.52.

Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol, and practically insoluble in water.

The approved use of DIFFERIN Solution is for the topical treatment of acne vulgaris. Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris.

The approved product is marketed in both a 30 ml and a 60 ml glass bottle with applicator. The applicator is designed so that the solution may be applied directly to the involved skin. The solution may be stored at controlled room temperature of 20°-25°C (68°-77°F).

## II. APPLICABLE FEDERAL STATUTE

The approved product, DIFFERIN Solution, was subject to regulatory review under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("the Act").

## III. PRODUCT APPROVAL DATE

The approved product, DIFFERIN solution, received permission for commercial marketing or use under Section 505 of the Act on May 31, 1996.

## IV. IDENTIFICATION OF DRUG PRODUCT INGREDIENTS

In accordance with 37 C.F.R. §1.740(a)(4), the active ingredient of DIFFERIN Solution is adapalene, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene has not been previously approved for commercial marketing or use under the Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

## V. APPLICATION FILING DEADLINE

The present application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last day on which the application can be submitted is July 29, 1996.

## VI. PATENT FOR WHICH EXTENSION IS SOUGHT

The patent for which an extension is being sought is U.S. Patent No. 5,212,303, which issued on May 18, 1993, in the names of Braham Shroot, Jacques Eustache and Jean-Michel Bernardos. The patent is assigned of record to Centre International de Recherches Dermatologiques (CIRD), Valbonne, France. Since this patent issued before June 8, 1995, the effective date of the Uruguay Round Agreements Act it is entitled to a patent term of the longer of twenty (20) years from the application filing date or seventeen (17) years from the patent issue date. For the '303 Patent, a patent term of

seventeen (17) years from the patent issue date of May 18, 1993, is longer. The patent would thus expire on May 18, 2010.

## VII. COPY OF PATENT

A copy of U.S. Patent No. 5,212,303 is enclosed herewith as Appendix A, including the entire specification and claims.

## VIII. COPY OF CERTIFICATE OF CORRECTION, DISCLAIMERS, MAINTENANCE FEE PAYMENT RECEIPTS OR REEXAMINATION CERTIFICATES

There is no certificate of correction, disclaimer, reexamination certificate or maintenance fee payment receipts for this patent.

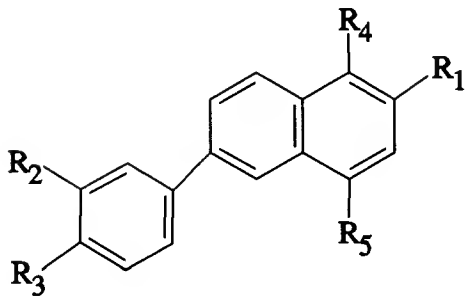
## IX. SHOWING THAT PATENT CLAIMS APPROVED PRODUCT

U.S. Patent No. 5,212,303 claims a process for preparing the active ingredient of the approved DIFFERIN product.

The following patent claims read directly on the approved product:

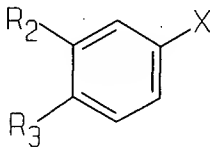
Claim 1 reads on the approved product. Claim 1 recites as follows:

1. A process for preparing a compound having the formula

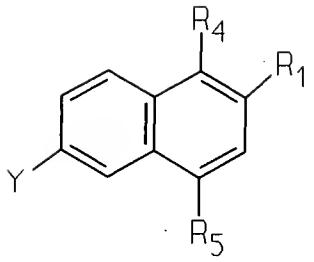



(I)

comprising coupling, in an anhydrous solvent and in the presence of, as a reaction catalyst, a transition metal or a complex thereof, a magnesium, lithium or zinc derivative of a compound of the formula

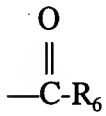



with a halogenated naphthalene compound of the formula



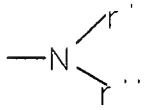

wherein

$R_1$ represents(I)



or (ii) —$CH_2OH$,

$R_6$ represents



or $OR_7$ wherein $R_7$ represents hydrogen, alkyl having 1-20 carbon atoms, monohydroxylalkyl or polyhydroxyalkyl, r' and r" represent hydrogen, lower alkyl, mono or polyhydroxyalkyl aryl or a residue of an amino acid, glucosamine, galactosamine or mannosamine, or together form a heterocycle selected from the group consisting of piperidino, piperazino, morpholino and pyrrolidino,

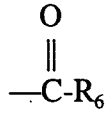
$R_2$ represents hydrogen, branched or straight chain alkyl 1-15 carbon atoms, alkoxy having 1-4 carbon atoms or a cycloaliphatic radical,

$R_3$ represents hydrogen, hydroxy, branched or straight chain alkyl having 1-4 carbon atoms, alkoxy having 1-10 carbon atoms, cycloaliphatic radical optionally substituted, a thiocycloaliphatic radical, or $—O—Si(CH_3)_2—R_8$ where $R_8$ represents linear of branched lower alkyl, provided that at least one of $R_2$ and $R_3$ is adamantyl or adamantylthio and

$R_4$ and $R_5$ each independently represent hydrogen, lower alkyl, hydroxy or lower acyloxy,

X and Y represent Cl, Br, F or I.

Adapalene, having the chemical formula as set forth in Appendix B, is a compound of formula (I), wherein $R_1$ is



wherein $R_6$ is $OR_7$ and $R_7$ is hydrogen, $R_2$ is a cycloaliphatic radical, $R_3$ is an alkoxy having 1-10 carbon atoms, and $R_4$ and $R_5$ are each hydrogen. Since DIFFERIN Solution contains adapalene, which is a compound prepared by the process of claim 1, claim 1 reads on the approved product.

Claim 2 also reads on the approved product. The process for preparing adapalene can be "carried out at a temperature ranging from -20° to +30°C", as recited in claim 2.

X. INFORMATION PURSUANT TO 35 U.S.C. §156(g)

The information required by 37 C.F.R. §1.740(a)(10)(v) is set forth below.

An Investigational New Drug (IND) application was filed by Dermatological Products of Texas, Inc. (formerly known as Dermatological Products of Texas, Inc., which company Galderma contracts with for the production and control of drug products under investigational development), for 6-[3-(1-adamantyl)-4-methoxyphenyl-2-naphthoic acid on August 18, 1988, and was received by the FDA on August 19, 1988. The IND became effective on September 18, 1988, thirty (30) days after the date of receipt of the IND. The IND number assigned to 6-[3-(1-adamantyl)-4-methoxyphenyl-2-naphthoic acid was IND 31,997.

A New Drug Application (NDA) was filed by Galderma Laboratories, Inc. (previously known as Owen/Galderma Laboratories, Inc.), on March 19, 1993. The NDA number assigned to the application for DIFFERIN Solution was NDA 20-338. The NDA was approved on May 31, 1996.

Further, the above identified patent is eligible for an extension of patent term, since the following requirements of §156(g) are met:

(1) the above identified patent has not expired prior to the filing of this application for extension of patent term;

(2) the term of the patent has never been extended;

(3) the application for extension of patent term is being submitted by the patent attorney or agent for the owner of record of the above identified U.S. Patent No. 5,212,303 for which a patent term extension is sought, authorized to practice before the U.S. Patent and Trademark Office, who has general authority from said owner to act on behalf of said owner in patent matters including the execution of the APPLICATION FOR EXTENSION OF PATENT TERM being submitted pursuant to 37 C.F.R. §1.740;

(4) the product has been subject to a regulatory review period before its commercial marketing or use in the United States;

(5) the permission for the commercial marketing or use of the product after such regulatory review period is the first such permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

## XI. ACTIVITIES DURING REGULATORY REVIEW PERIOD

Significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the dates applicable to such activities areas follows:

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| September 19, 1989 | Dr. Browder, Mr. Davitt and Dr. Osterberg of FDA met with sponsor representatives to discuss the nonclinical studies planned for submission in support of an NDA. |
| April 27, 1990 | A letter from Dr. Murray Lumpkin in which the agency concurred that the sponsor must provide precautionary labeling clearly stating that there have been positive findings relating to photocarcinogenicity for retinoids and related compounds. |
| November 7, 1990 | A pre-NDA meeting, which included Drs. Lumpkin, Burlington, Evans, Rand, Harkins and Ms. Cook of FDA and sponsor representatives. The focus of the meeting was to review the available clinical data from both U.S. and European studies and to assess the completeness of the clinical evidence of safety and efficacy towards making a determination of fileability of an NDA for the drug product. Based on several comments and concerns expressed by agency participants with regard to the one completed vehicle-controlled study, the sponsor elected to conduct an additional vehicle-controlled study (No. 9104-CD271L-EV), which was initiated in March of 1991, and completed in August of 1991. The submission of the NDA was based on the November 7, 1990 meeting discussions and the completion of the subsequent clinical study. |
| December 3, 1991 | A letter from Galderma reaffirming its commitment to include a statement the PRECAUTIONS section of the labeling, which closely followed the statement suggested in Dr. Lumpkin's April 27, 1990, letter. |

October 19, 1992 — Correspondence to IND 31,997 addressed the matter of submitting "line listings" for patients enrolled in pivotal clinical studies. T

December 14, 1992 — Galderma Laboratories, Inc., referred to herein as "the applicant", submitted the Chemistry, Manufacturing and Controls Data section of the NDA pursuant to the provisions of 21 CFR 314.50(d)(1)(iv).

March 19, 1993 — Original application submission of remaining sections following Pre-NDA Submission of Chemistry, Manufacturing and Controls Data on December 14, 1992. The application included the following:

**VOLUME 2.1**
- ITEM 1. INDEX
- ITEM 2. SUMMARY
- ITEM 4.c. LABELING

**VOLUMES 2.2 - 2.42**
- ITEM 5. NONCLINICAL PHARMACOLOGY and TOXICOLOGY SECTION

**VOLUMES 2.43 - 2.44**
- ITEMS 6. HUMAN PHARMACOKINETICS and BIOAVAILABILITY SECTION

**VOLUMES 2.45 - 2.61**
- ITEM 8. CLINICAL AND STATISTICAL DATA SECTION

**VOLUMES 2.62 - 2.66**
- ITEM 11. CASE REPORT TABULATIONS

**VOLUMES 2.67 - 2.68**
- ITEM 12. CASE REPORT FORMS

STATISTICAL APPENDIX VOLUMES I - III

March 22, 1993 — Desk copies of Volume 2.1 sent to Ms. Rosemary Cook, CSO, FDA.

April 20, 1993 — FDA Review Chemist's request for status of manufacturing facilities "inspection readiness.

April 26, 1993 — FDA Review Microbiologist's request for Microbial Limits Test data and-Procedure.

April 29, 1993 — Applicant's amendment to application in response to Microbiologist's request. Submitted MLA procedure and test results.

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| April 30, 1993 | FDA's request for administrative items to complete "filing review". |
| May 6, 1993 | Applicant's amendment to application in response to "filing review" items and Chemist's request for manufacturing facilities information. |
| May 11, 1993 | FDA's request for information to aid statistical reviewer in use of SAS Data Sets. May 12th memo of telephone call to FDA reviewer by M. Tuley verifying request. |
| May 12, 1993 | FDA's request for Microbial Limits Test data to demonstrate preparatory testing and validity of method. |
| May 21, 1993 | Applicant's amendment to application to provide information to statistical reviewer in partial response to May 11th request and a technical report on preparatory testing to validate the Microbial Limits Test in response to May 12th request. |
| June 7, 1993 | FDA telephone call. Request for copies of Chemistry, Manufacturing and Controls section sent to S.A. Inspection Post. Expressed objection to DIFFERIN trade name. |
| June 9, 1993 | Applicant's amendment to application providing:<br>1) SAS programs to Statistical Reviewer; and<br>2) Notification of transmittal of Item 3 & 4 Volumes and amendments to FDA San Antonio inspectors. Copy of letter to Mr. Martinez included. |
| June 11, 1993 | FDA telephone call from Dr. Elhage. Request for Desk Copy of Vol. 2.1 and information on Clinical Studies 9104-CD271L-EV and CR 88043. |
| June 16, 1993 | FDA facsimile transmission dated June 14 providing:<br>1) Chemistry review comments; and<br>2) Objection to DIFFERIN name. |
| June 22, 1993 | a) Submission of information to Dr. El Hage in response to his request of June 11, 1993.<br>b) Submission of documents to NDA File. |

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| June 30,1993 | Submission of documents and information to Mr. Martinez in response to inspection of Dermatological Products of Texas, Inc. ("DPT") manufacturing facilities. |
| July 1, 1993 | Response to facsimile transmission of June 14th, providing<br>1) Chemistry comments; and<br>2) Objection to tradename. |
| July 26, 1993 | Environmental Assessment review and request for additional information by FDA. |
| August 12, 1993 | Amendment in response to FDA 483 inspection observations. |
| August 26, 1993 | 4-Month Safety Update provided by Applicant. |
| September 17, 1993 | Response to Clinical Review comments on 9104-CD271L-EV from D. Bostwick. |
| September 17, 1993 | Facsimile transmission from D. Bostwick with request for tabulated data on clinical studies 9104-CD271L-EV, C-88-26 and C-88-27. |
| September 17, 1993 | M. Tuley memo to the file. FDA Statistician request for assistance with SAS datasets. |
| September 20, 1993 | M. Tuley facsimile transmission to FDA Statistician with Formats for Adapalene Solution Submission. |
| September 22, 1993 | M. Tuley memo to the file. Telephone conversation with Dr. Ralph Harkins on tables for clinical studies 9104-CD271L-EV, C-88-26 and C-88-27. |
| September 20, 1993 | Facsimile transmission from FDA with 10 Chemistry Review comments. |
| September 24, 1993 | Acknowledgment of Chemistry Review comments. Commitment to respond by October 29, 1993. |
| September 24, 1993 | Submission of Clinical Statistical Data Tables for 9104-CD271 L-EV. |

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| September 29, 1993 | Submission of Clinical Review Responses (see Tab 2-September 17, 1993) and Diskette of SAS Codes to Statistician Dr. Srinivasan. |
| October 5, 1993 | M. Tuley memo to the file. Telephone conversation of September 30 with D. Bostwick and Dr. Srinivasan. D. Bostwick has recommended approval based on Clinical and Statistical review. |
| October 27, 1993 | Facsimile transmission to R. Cook, FDA, setting forth a commitment for responses to Chemistry Review Comments. |
| October 29, 1993 | Additional Statistical data and diskette as requested by Dr. Srinivasan |
| October 29, 1993 | Volume 1 of 2 - response to FDA chemistry review comments received 9-20-93. Volume 2 of 2 -methods validation package with new and revised procedures. |
| November 1, 1993 | Submission of Field Copy to FDA Dallas District Office. |
| November 24, 1993 | Applicant Submitted:<br>(1) Completed response to FDA Chemistry review comments of September 20, 1993. Analytical methods for THF and Chromatographic Purity in raw material. DPT procedures for alcohol and adapalene in drug product. New lists of Tests, Specifications and Methods for drug substance, finished product and Post-Approval Stability Studies; and<br>(2) Comprehensive resubmission of Methods Validation Package |
| December 3, 1993 | Environmental Assessment resubmission |
| December 7, 1993 | Facsimile transmission to Ms. R. Cook on status of application. |
| December 8, 1993 | Facsimile transmission from Mr. Timper, Chemist, asking two questions regarding: 1) status of EA submission, and 2) availability of impurity samples |
| December 10, 1993 | Response submitted to NDA with facsimile transmission copies to Mr. Timper and Ms. Cook |
| January 5, 1994 | FDA Notification of intent to inspect FINORGA |

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| January 10, 1994 | Submission of DPT permit information for EA requested by Dr. Tso. |
| January 17, 1994 | Submission of French and Irish Labeling and notification of pending facilities inspections. |
| January 31, 1994 | Submission of U.S. Clinical Studies Data Tables - Summary without patients on oral antibiotics. |
| February 23, 1994 | Facsimile transmission to R. Cook on status of pending activities: a) FINORGA inspection, b) DPT re-inspection, and c) Pre-clinical review. |
| February 28, 1994 | Safety Update, including status of worldwide marketing applications. |
| March 2, 1994 | Facsimile transmission to R. Cook on submission of pathology (tumor) data. Letter of Authorization for Pharmaco::LSR to submit electronic data to Dr. Lin. |
| February 24, 1994 | FDA extension of user fee date to June 24, 1994. |
| March 14, 1994 | Facsimile transmission to R. Cook on submission of pathology (tumor) data by Pharmaco:: LSR on March 11. Update on FINORGA and DPT inspections. |
| March 18, 1994 | Pre-Clinical - Submission of Pharmaco::LSR support documentation and correspondence to Dr. Lin in re: pathology (tumor) data from carcinogenicity studies. |
| April 1, 1994 | DPT inspection notification February 22 - March 11, 1994 and March 16, 1994 FDA 483. DPT March 29th response submission. |
| April 4, 1994 | April 1994 - Draft labeling submitted by Applicant |
| April 15, 1994 | Telephone call from Ms. R. Cook, informing Applicant that preclinical biostatistical review was completed. |
| April 26, 1994 | Submission of FINORGA response to 483 |
| April 26, 1994 | Facsimile transmission to R. Cook on status of application |

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| May 20,1994 | Submitted draft labeling, incorporating FDA recommended revisions |
| May 25,1994 | Telephone conversation with R. Cook and Dr. Chambers regarding FDA Draft Labeling |
| May 27,1994 | Facsimile transmission to R. Cook |
| May 24,1994 | FDA Laboratory review comments and recommendations for procedure modifications |
| June 3, 1994 | Submission of revised draft labeling |
| June 6, 1994 | Facsimile transmission to R. Cook on status of application |
| June 15, 1994 | CMC Amendment submitted by Applicant<br>- FINORGA response to FDA letter dated 5/9/94<br>- Sponsor response to 5/24/94 facsimile transmission of FDA Testing Laboratory comments. (Includes new and revised DFT procedures and Drug Product assay validation.) |
| June 17, 1994 | Facsimile transmission to Ms. Rosemary Cook with status of submission amendments |
| September 2, 1994 | Methods Validation Package for Drug Product. Copy submitted to Mr. Jim Hanus FDA Testing laboratory DDO. |
| November 10, 1994 | Facsimile transmission to Rosemary Cook requesting status of application.<br><br>Amendment with FINORGA responses to September 29-30th Form 483 inspection and CIRD technical report on identification of IM2 impurity. |
| December 15, 1994 | Facsimile transmission to Rosemary Cook requesting status of application. |
| January 4, 1995 | Facsimile transmission to Rosemary Cook requesting status of application. |

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| January 12, 1995 | Facsimile transmission to Rosemary Cook with amendment summary for status determinations |
| February 21, 1995 | Amendment with update of Foreign approvals and Canadian Product Monograph. |
| March 21, 1995 | Letter to Rosemary Cook regarding reinspection of FINORGA. |
| May 1, 1995 | CMC Amendment to correct all outstanding deficiencies. Request for change in frosted bottle to nonfrosted and FINORGA Process validation report. |
| May 10, 1995 | Facsimile transmission from J. Timper advising review of FINORGA DMF update. |
| July 6, 1995 | Patent Information submission per URAA |
| March 29, 1996 | FDA Nomenclature Committee review of DIFFERIN Tradename. |
| May 29, 1996 | Facsimile transmission to FDA with revised draft package insert labeling. |
| May 30, 1996 | Amendment with final draft labeling. |
| May 31, 1996 | FDA Approval Letter. |

## XII. ELIGIBILITY OF PATENT FOR EXTENSION

In the opinion of Applicant, the above identified patent is eligible for an extension of the term for 13 days, and to thus expire on May 31, 2010. The length of the claimed extension of 13 days was determined by Applicant, pursuant to 37 C.F.R. §1.775, to be fourteen years from the date of the FDA final approval, as described below:

### A. Length of the Regulatory Review Period (Rule 775(c))

*1. Period Pursuant to Paragraph (c)(1)*

The period defined at 37 C.F.R. §1.775(c)(1) began on September 18, 1988 (the date the IND became effective) and ended on March 19, 1993 (the date the NDA was filed). The (c)(1) period is thus 1643 days.

*2. Period Pursuant to Paragraph (c)(2)*

The period defined at 37 C.F.R. §1.775(c)(2) began March 19, 1993 (the date of submission of the NDA submitted pursuant to Section 505(b) of the Act) and ended May 31, 1996 (the commercial marketing and use approval date). The (c)(2) period is thus 1169 days.

The total (c)(1) and (c)(2) time period is thus 2812 days.

B. Term of the Patent as Extended (Rule 775(d))

The term of the patent as extended was then calculated to expire on October 30, 2015, pursuant to 37 C.F.R. §1.775(d).

*1. (d)(1) Period (Days Subtracted from Regulatory Review Period)*

The regulatory review period upon which the period of extension is calculated by subtracting from the regulatory review period as determined in (c)(1) and (c)(2) of this section the following:

*(I) The number of days in the periods of paragraphs (c)(1) and (c)(2) above which were on or before January 5, 1988, the issue date of the original patent.*

Since no days in the periods of paragraphs (c)(1) and (c)(2) were on or before January 5, 1988, the number of days to be subtracted from the regulatory review period is zero.

*(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) during which the Applicant did not act with due diligence.*

In Applicant's opinion, marketing applicant acted with due diligence as defined at 35 U.S.C. §156(d)(3) during the above calculated periods of paragraphs (c)(1) and (c)(2). Accordingly, zero days are subtracted from the regulatory review period.

*(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(I) and (ii) of this section (ignoring half days).*

There are 1643 days in the period defined by paragraph (c)(1). Since there are no reductions in this time period pursuant to paragraphs (d)(1)(I) and (ii) of this section, the number of days remaining in the period defined by paragraph (c)(1) is 1643 days. One-half of 1643 days, ignoring half days for purposes of subtraction, is 821. Subtracting 821 days from 2812 results in a time period of 1991 days.

Thus, the period determined according to paragraph (d)(1) is 1991 days.

*2. (d)(2) Date*

The number of days determined in paragraph (d)(1), 1991 days, added to the original term of the patent, i.e., 17 years from the issue date, results in an extended patent expiration date of October 30, 1015.

*3. (d)(3) Date*

Fourteen years added to the May 31, 1996, date of approval under the Federal Food, Drug and Cosmetic Act, yields an extended patent expiration date of May 31, 2010.

*4. (d)(4) Date*

Comparing the extended terms determined according to paragraphs (d)(2) and (d)(3), the earlier date is May 31, 2010.

*5. (d)(5) Date*

The original patent issued after September 24, 1984. Five years added to the original expiration date of the patent is May 18, 2015.

By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(I) of this section with each other, the earlier date is May 31, 2010.

*6. (d)(6) Date*

The original patent was issued after September 24, 1984. This section thus does not apply.

## XIII. ACKNOWLEDGMENT OF DUTY TO DISCLOSE

Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought pursuant to 37 C.F.R. §1.765.

## XIV. APPLICATION FEE

Applicant submits herewith a check for $1060.00 in payment of the fee set forth at 37 C.F.R. §1.20(j).

The Commissioner is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to deposit Account No. 02-4800.

## XV. CORRESPONDENCE ADDRESS

Please direct all correspondence and inquiries regarding this matter to:

Norman H. Stepno
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404
Phone: (703) 836-6620

## XVI. DUPLICATE OF APPLICATION AND CERTIFICATION

Applicant encloses herewith a copy of the present application papers, and certifies that said copy is a duplicate of the application papers. For the convenience of the Senior Legal Advisor of the Patent Office, Applicant is also enclosing three (3) additional copies of the application.

XVII. DECLARATION

A Declaration pursuant to 37 C.F.R. §1.740(b) is attached hereto.

In view of the foregoing, an extension of the term of the above identified patent is respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____

Norman H. Stepno
Registration No. 22,716
Donna M. Meuth
Registration No. 36,607

Post Office Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

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Patent
Attorney's Docket No. 010095-003e

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re Patent of | ) | |
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| Braham Shroot, et al | ) | |
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| U.S. Patent No.: 5,212,303 | ) | Attn: Box Patent Extension |
| | ) | |
| Issued: May 18, 1993 | ) | |
| | ) | |
| For: BENZONAPHTHALENE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND THEIR USE IN THERAPEUTIC AND COSMETIC COMPOSITIONS | ) | |

**DECLARATION UNDER 37 C.F.R. §1.740(a)(17)**

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

I, Donna M. Meuth, do hereby declare as follows:

I am a patent attorney or agent for the owner of record of the above identified U.S. Patent No. 5,212,303 for which a patent term extension is sought, authorized to practice before the U.S. Patent and Trademark Office, and have general authority from the owner to act on behalf of the owner in patent matters, including the execution of the APPLICATION FOR EXTENSION OF PATENT TERM being submitted pursuant to 37 C.F.R. §1.740.

I have reviewed and understand the contents of the application being submitted herewith.

I believe that the patent is subject to extension pursuant to 37 C.F.R. §1.710.

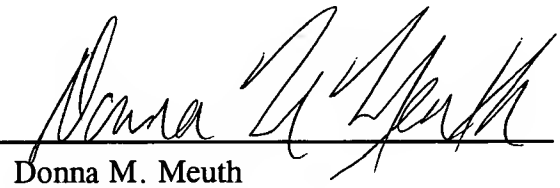
I believe that an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations.

I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 

Donna M. Meuth
Registration No. 36,607

Post Office Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: July 26, 1996

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# United States Patent [19]

Shroot et al.

[11] Patent Number: 5,212,303

[45] Date of Patent: May 18, 1993

[54] BENZONAPHTHALENE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND THEIR USE IN THERAPEUTIC AND COSMETIC COMPOSITIONS

[75] Inventors: Braham Shroot, Antibes; Jacques Eustache, Grasse; Jean-Michel Bernardon, Nice, all of France

[73] Assignee: Centre International de Recherches Dermatologiques (CIRD), Valbonne, France

[21] Appl. No.: 952,341

[22] Filed: Sep. 28, 1992

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[30] Foreign Application Priority Data

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[51] Int. Cl.[5] ..... C07D 265/30; C07D 211/06; C07C 7/02

[52] U.S. Cl. ..... 544/69; 544/158; 544/176; 544/209; 544/386; 544/391; 546/14; 546/205; 546/206; 548/406; 548/539; 560/56; 560/100; 562/467; 562/490

[58] Field of Search ..... 544/69, 158, 176, 209, 544/386, 391; 546/14, 205, 206; 548/406, 539; 560/56, 100; 562/467, 490

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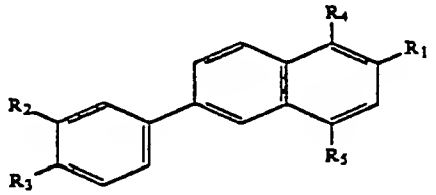
*Primary Examiner*—Johann Richter

*Attorney, Agent, or Firm*—Cushman, Darby & Cushman

[57] ABSTRACT

A benzonaphthalene compound has the formula



(I)

wherein $R_1$ represents (i)

or (ii) —$CH_2OH$; $R_6$ represents

or $OR_7$ wherein $R_7$ represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' or r'' represent hydrogen, lower alkyl, mono or polyhydroxyalkyl, aryl or a residue of an amino acid or a sugar, or together form a heterocycle; $R_2$ represents hydrogen, alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic radical; $R_3$ represents hydrogen, hydroxy, alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic radical, a thiocycloaliphatic radical or —O—$Si(CH_3)_2$—$R_8$ wherein $R_8$ represents lower alkyl; and $R_4$ and $R_5$ represent hydrogen, lower alkyl, hydroxy or lower acyloxy.

This compound is useful in the topical and systemic treatment of dermatologic diseases and in the treatment of the degeneration of conjuctive tissues. The compound also possesses anti-tumor acitivity.

2 Claims, No Drawings

# BENZONAPHTHALENE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND THEIR USE IN THERAPEUTIC AND COSMETIC COMPOSITIONS

This is a division of application Ser. No. 07803,965, filed Dec. 9, 1991, now U.S. Pat. No. 5,183,889 which is a division of Ser. No. 07502/122, filed Mar. 30, 1990, now U.S. Pat. No. 5,098,895, which is a division of Ser. No. 07/120,968, filed Nov. 16, 1987, now U.S. pat. No. 4,861,229, which is a division of Ser. No. 06/850,145, filed Apr. 10, 1986, now U.S. Pat. No. 4,717,720.

The present invention relates to benzonaphthalene derivatives, to a process for preparing them and to their use in therapeutic and cosmetic compositions.

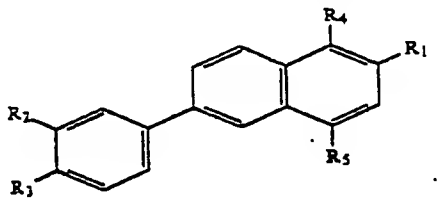
These new benzonaphthalene derivatives are usefully employed in the topical and systemic treatment of dermatological diseases linked to keratinization disorders (differentiation—proliferation) and dermatological diseases, or others, with inflammatory and/or immunoallergic components and in the treatment of diseases attributable to the degeneration of conjuctive tissue. The benzonaphthalene derivatives of the present invention also exhibit anti-tumor activity. Moreover, these derivatives can be employed in the treatment of atopy be it cutaneous or respiratory.

The benzonaphthalene derivatives of the present invention are also usefully employed in the field of ophthalmology and principally in the treatment of corneopathies.

A number of compounds have already been proposed for the various treatments noted above and principally compounds known under the designation of "retinoids" of which the most well-known ones are the trans and cis retinoic acids (tretinoin and isotretinoin) and etretinate.

Compared to these known compounds, the benzonaphthalene derivatives according to the present invention exhibit a strong activity and better stability to light and to oxygen of the air.

The benzonaphthane derivatives of the present invention can be represented by the following formula:




(I)

wherein

$R_1$ represents:

(i)

or (ii) $-CH_2OH$,

$R_6$ represents



or $-OR_7$ wherein $R_7$ represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' and r" represent hydrogen, lower alkyl, mono- or polyhydroxyalkyl, aryl optionally substituted or a residue of an amino acid or aminated sugar or r' and r" taken together form a heterocycle,

$R_2$ represents hydrogen, branched or straight chain alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic group,

$R_3$ represents hydrogen, hydroxy, straight or branched chain alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic group substituted or not, a thio-cycloaliphatic group or a group of the formula $-O-Si(CH_3)_2-R_8$ wherein $R_8$ represents linear or branched lower alkyl,

$R_4$ and $R_5$ each independently represent hydrogen, lower alkyl, hydroxy or a lower acyloxy group, and the salts of the said benzonaphthalene derivatives of Formula I.

By the expression "lower alkyl" is meant alkyl radicals having from 1–6 carbon atoms and principally methyl, ethyl, isopropyl, butyl and tert.butyl.

The term "alkoxy" is intended to include radicals having 1–10 carbon atoms and principally methoxy, ethoxy, isopropoxy, hexyloxy and decyloxy radicals.

By the expression "lower acyloxy" is meant radicals having 1–4 carbon atoms and principally acetyloxy and propionyloxy radicals.

By the term "monohydroxyalkyl" is meant a monohydroxy substituted radical having 2 or 3 carbon atoms, principally, 2-hydroxy ethyl and 2-hydroxypropyl.

Representative residues of aminated sugars include those derived from glucosamine, galactosamine and mannosamine.

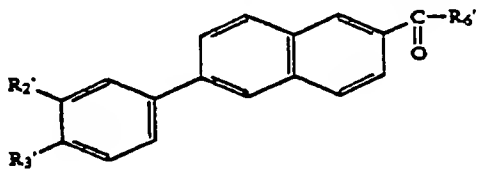
By the term "polyhydroxyalkyl" is meant an alkyl radical having 3–6 carbon atoms substituted 2–5 hydroxyl groups, such as 2,3-dihydroxy propyl, 1,3-dihydroxy propyl, or the residue of pentaerythritol.

The term "cycloaliphatic" is meant to include a mono or polycyclic radical such as, for example, 1-methyl cyclohexyl or 1-adamantyl.

The preferred thiocycloaliphatic radical is, principally, 1-adamantylthio.

When r' and r" together form a heterocycle, it is preferably a piperidino, piperazino, morpholino or pyrrolidino radical.

The preferred compounds of Formula I are more particularly those having the following formula:




(II)

wherein

$R'_6$ represents

or $-OR'_7$,

r' and r'' each independently represent hydrogen or lower alkyl, or r' and r'' taken together form a morpholino radical,

$R'_7$ represents hydrogen or lower alkyl,

$R'_2$ represents hydrogen, alkyl, alkoxy or 1-adamantyl, and

$R'_3$ represents hydrogen, hydroxy, alkyl, alkoxy or 1-adamantylthio.

Representative compounds of the present invention include:

(1) 6-(3-methylphenyl)-2-naphthoic acid and its methyl ester,

(2) 6-(4-tert.butyl phenyl)-2-naphthoic acid and its methyl ester,

(3) 6-(3-tert.butyl phenyl)-2-naphthoic acid and its methyl ester,

(4) 6-(3,4-dimethoxy phenyl)-2-naphthoic acid and its methyl ester,

(5) 6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid and its methyl ester,

(6) 6-[3-(1-adamantyl)-4-methoxyphenyl-2-naphthoic acid and its methyl ester,

(7) the methyl ester of 6-[3-(1-adamantyl)-4-tert-.butyldimethylsilyloxyphenyl]-2-naphthoic acid,

(8) the methyl ester of 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid,

(9) 6-[3-(1-adamantyl-4-hydroxyphenyl]-2-naphthoic acid,

(10) the methyl ester of 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid,

(11) 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid,

(12) the methyl ester of 6-[3 TM (1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid,

(13) 6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid,

(14) the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-acetoxy-1-methyl-2-naphthoic acid,

(15) 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy 1-methyl-2-naphthoic acid,

(16) the methyl ester of 6-[3-(1-adamantyl)-4-methoxy-phenyl]-4-hydroxy-1-methyl-2-naphthoic acid,

(17) the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid,

(18) 6-[3-(1-adamantyl)-4-methoxypheny l]-1-methyl-2-naphthoic acid,

(19) 6-[3-(1-adamantyl 4-methoxyphenyl]-2-naphthalene methanol,

(20) the ethylamide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid,

(21) the morpholide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid,

(22) the methyl ester of 6-[3-tert.butyl-4-methoxyphenyl]-2-naphthoic acid,

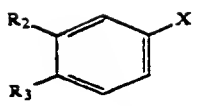
(23) 6-(3-tert.butyl-4-methoxyphenyl)-2-naphthoic acid,

(24) the methyl ester of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid, and

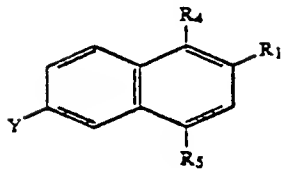
(25) 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid.

The present invention also relates to a process for preparing the compounds of Formula I.

According to this process the compounds of Formula I are obtained by a coupling reaction between a halogenated compound of Formula III and a halogenated derivative of naphthalene of Formula IV:




(III)




(IV)

wherein

$R_1$ to $R_5$ have the same meanings as those given above for Formula I and

X and Y represent Cl, Br, F or I.

According to this coupling reaction, the halogenated compound of Formula III is transformed into its magnesium, lithium or zinc form in accordance with methods described in the literature and is coupled with the halogenated naphthalene derivative of Formula IV by employing, as a reaction catalyst, a transition metal or one of its complexes.

Particularly preferred catalysts are those derived from nickel or palladium and more particularly the compounds of $Ni_{II}$ ($NiCl_2$) with various phosphines.

The coupling reaction is generally carried out at a temperature between −20° and +30° C. in an anhydrous solvent such as, for example, dimethylformamide or tetrahydrofuran.

The resulting product can be purified by recrystallization or silica column chromatography.

Obviously, the choice of the halogenated naphthalene derivative of Formula IV, for use in the coupling reaction with the halogenated compound of Formula III, must be such that it can lead, by subsequent reaction, to the various meanings of the $R_1$ radical given above.

When the compounds according to the present invention are provided in salt form, it is a question of salts of an alkali or alkaline earth metal or of an organic amine when the compounds have at least one free acid function.

The present invention also relates to a medicinal composition comprising as the active principle thereof the compounds of Formula I as defined above.

These compounds exhibit excellent activity in the test for inhibiting ornithine decarboxylase after induction, by "tape stripping" the body of a nude rat. This test is considered a measure of the activity of the retinoids with regard to cellular proliferation phenomenon.

For instance, it has been noted that in this test, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid exhibits an effective dose between 5 and 25 nmoles applied per $cm^2$.

The compounds according to the invention also exhibit a strong activity in the differentiation test of embryonic tetracarcinoma F9 rat cells (Cancer Research 43, page 5268, 1983).

As an illustration, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid, at a 0.01 micromolar concentration induces the differentiation of F9 carcinoma cells in endoderm cells.

6-(3-tert.butyl phenyl)-2-naphthoic acid acts in the same fashion at a concentration of 1 micromolar.

Moreover, the irritation test carried out on a rabbit has shown that the compounds of Formula I are less irritating than known retinoids of analogous structure. Moreover, their acute toxicity is weaker.

The compounds of the present invention are indeed particularly suitable for the treatment of dermatological diseases linked to a keratinization disorder (differentiation, proliferation), as well as dermatological diseases or others with inflammatory and/or immunoallergic components such as principally:

acne vulgaris, comedons or polymorphs, solar acne seniles and medicamental or professional acne;

extensive and/or severe forms of psoriasis, and other keratinization disorders, and principally ichtyosis and ichtyosiform states;

Darier disease;

palmo-plantary keratodermy;

leucoplasies and leucoplasiform states, lichen plan;

all dermatological proliferations, benign or malignant, severe or extended.

They are also active for certain rheumatic diseases principally psoriasic rheumatism, for cutanerus or respiratory atopies, as well as for certain ophthalmologic disorders relative to the corneopathies.

The present invention also relates to medicinal compositions containing at least one compound of Formula I, as defined above and/or a salt thereof.

The present invention thus relates to a new medicinal composition, intended principally for the treatment of the above-mentioned diseases, comprising in a pharmaceutically acceptable support, at least one compound of Formula I and/or a salt thereof.

As has been indicated previously, the berzonaphthalene derivatives according to the present invention, relative to known retinoids, exhibit better stability against light and oxygen, this being essentially due to the fact that they do not possess any easily isomerized double bonds.

The compounds according to the present invention are generally administered at a daily dosage of about 2 μg/kg to 2 mg/kg of body weight.

As vehicles or supports for these compositions, there can be employed any conventional support, the active compound being found either in the dissolved state or in the dispersed state in the vehicle or support.

The composition can be administered enterally, parenterally, topically or ocularly. When administered enterally, the medicinal composition can be provided in the form of tablets, gelules, lozenges, syrups, suspension, solutions, powders, granules or emulsions. When administered parenterally the medicinal composition can be provided in the form of solutions or suspensions for perfusion or injection.

When administered topically, the pharmaceutical compositions based on the compounds in accordance with the present invention can be provided in the form of ointments, tinctures, creams, pommades, powders, impregnated pads, buffers, solutions, lotions, gels, sprays or even suspensions.

These compositions for topical application or administration can be provided either under anhydrous form, or in aqueous form according to clinical indications. When administered ocularly, the compositions are principally eyewashes.

The topical or ocular composition contains preferably between 0.0005 and 5 weight percent of the active compound based on the total weight of the composition.

The compounds of Formula I, according to the present invention also find use in the cosmetic field, in particular in body and hair hygiene and principally for acne, hairgrowth, preventing hair failout, to combat against the oily appearance of the skin or hair, in the protection against harmful effects of the sun or in the treatment of physiologically dry skin.

The present invention then also envisages a cosmetic composition containing in a cosmetically acceptable support at least one compound of Formula I and/or a salt thereof, this composition being provided principally in the form of a lotion, gel, soap or shampoo.

The concentration of the compound(s) of Formula I in the cosmetic compositions is between 0.0005 and 2 weight percent, preferably between 0.01 and 1 weight percent, based on the total weight of the composition.

The medicinal and cosmetic compositions according to the present invention can contain inert or even pharmacodynamic or cosmetically active adjuvants and principally: hydrating agents such as thiamorpholinone and its derivatives or urea; antiseborrheic agents such as S-carboxymethylcysteine, S-benzyl cysteamine and their derivatives, or tioxolone; antibiotics such as erythromycin, neomycin or the tetracyclines; agents favoring hair growth such as "Minoxidil" (2,4-diamino-6-piperidinopyrimidine-3-oxide) and its derivatives, Diazoxide and Phenytoin; steroidal anti-inflammatory agents; carotenoids and principally β-carotene; and antipsoriasic agents such as anthralin and its derivatives, 5,8,11,14-eicosatetrainoic acid and 5,8,11-triynoic acid.

The compositions according to the present invention can also contain flavor improving agents, preservatives, stabilizers, humidity regulating agents, pH regulating agents, osmotic pressure modifying agents, emulsifiers, UV-A and UV-B filters and antioxidants such as α-tocopherol, butylhydroxy anisole or butylhydroxy toluene.

The following non-limiting examples illustrate several examples for the preparation of the active compounds of Formula I according to the present invention, as well as examples of compositions containing these active compounds.

## EXAMPLE 1

Methyl ester of 6-(3-methylphenyl)-2-naphthoic acid. Compound of Formula II wherein $R'_3$=H and $R'_2$=—$CH_3$ and $R'_6$=—$OCH_3$

342 mg (2 mmol) of 3-bromotoluene in 4 ml of THF are converted into the corresponding magnesium form and then treated with an equivalent of zinc chloride to provide the corresponding zinc derivative. There are successively added 310 mg (1.17 mmol) of methyl 6-bromo-2-naphthoate and 10 mg (0.02 mmol) of $NiCl_2$/1,2-(diphenylphosphino)ethane—DPPE—as the catalyst. The reaction mixture is stirred at ambient temperature for 30 minutes and the mineral salts are then removed by passing the reaction mixture through a 2 × 3 cm silica column. The reaction mixture is then evaporated to dryness and the residue is chromatographed (HPLC column—Zorbax sil), using as the eluant, a mixture of cyclohexane (75%) and ether (25%). The product thus recovered has an Rf=0.45 (silica plate, eluant: hexane 50%, dichloromethane 50%) and crystallizes on evaporation of the chromatography solvents. The yield is 84%. Melting point—107° C.

## EXAMPLE 2

Methyl ester of 6-(4-tert.butyl phenyl)-2-naphthoic acid. Compound of Formula II wherein $R'_2$=H, $R'_3$=—$C(CH_3)_3$ and $R'_6$=—$OCH_3$

In a manner analogous to Example 1, starting with 639 mg (3.0 mmol) of 4-bromo tert.butyl benzene and 465 mg (1.75 mmol) of methyl 6-bromo-2-naphthoate, 0.30 g of the expected product is obtained. Yield—54%. Melting point—154° C.

## EXAMPLE 3

Methyl ester of 6-(3-tert.butyl phenyl)-2-naphthoic acid. Compound of Formula II wherein $R'_3$=H, $R'_2$=—$C(CH_3)_3$ and $R'_6$=—$OCH_3$

3.50 g (16.4 mmol) of 3-tert.butyl bromotenzene are added to a suspension of magnesium (0.44 g —18 m Atg) in 20 ml of dry tetrahydrofuran. The reaction is initiated by addition of an iodine crystal and continued at 50° C. for 30 minutes.

2.46 g (18 mmol) of anhydrous zinc chloride dissolved in 20 ml of dry tetrahydrofuran are then added and after 15 minutes, the reaction mixture is cooled to 0° C. At this point, 3.63 g (13.7 mmol) of methyl 6-bromo-2-naphthoate and 86 mg (0.26 mmol) of the $NiCl_2$/DPPE complex are added to the reaction mixture.

After stirring for 1 hour at ambient temperature, 100 ml of water are added and the mixture is extracted with ether. After washing the organic phase with a saturated solution of sodium bicarbonate, and water, then drying (sodium sulfate) and evaporating the solvents, the resulting residue is recrystallized in heptane. 3.12 g of the methyl ester of 6-(3-tert.butyl phenyl)-2-naphthoic acid which melts at 138° C. are obtained.

## EXAMPLE 4

6-(3-tert.butyl phenyl)-2-naphthoic acid. Compound of Formula II wherein $R'_3$=H, $R'_2$=—$C(CH_3)_3$ and $R'_6$=OH.

1.0 g (3.14 mmol) of the methyl ester of 6-(3-tert.butyl phenyl)-2-naphthoic acid obtained in Example 3 is added to a mixture of 95% ethanol (40 ml) and soda (4 ml, 5N).

The mixture is heated at 60° C. for 2 hours at which point 50 ml of water are added and the mixture is acidified to pH 1 with 2N HCl. The acidified mixture is then extracted with ether and the organic phase is washed with water until neutral. After drying (sodium sulfate) and evaporation of the solvent, 6-(3-tert.butyl phenyl)-2-naphthoic acid (900 mg) which sublime 190° C. is obtained.

## EXAMPLE 5

Methyl ester of 6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid. Compound of Formula II wherein $R'_2$=H, $R'_3$=1-adamantylthio and $R'_6$=—$OCH_3$

(a) p-(1-adamantylthio) bromobenzene.

3.78 g (20 mmol) of p-bromothiophenol, 3.04 g (20 mmol) of 1-adamantanol and 10 ml of trifluoroacetic acid are stirred at ambient temperature for 8 hours and then poured into water. Sodium bicarbonate is added until the mixture is neutral at which time it is extracted with methylene chloride. The organic phase is dried and evaporated. After recrystallization in isooctane, 5.9 g of the expected product are obtained. Yield—92%. Melting point: 121°–122° C.

(b) Methyl ester of 6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid

0.64 g (26.5 m Atg) of magnesium suspended in 10 ml of tetrahydrofuran (THF) are treated slowly with 5.7 g (17.6 mmol) of p-(1-adamantylthio) bromobenzene. After heating at reflux for 2 hours and cooling to 20° C., 2.4 g (17.6 mmol) of anhydrous Zn $Cl_2$ are added. The mixture is stirred for one hour at 20° C. at which point 2.8 g (10.4 mmol) of methyl 6-broxo-2-naphthoate are added and then 92 mg of $NiCl_2$/1,2-(diphenylphosphino)ethane-DPPE complex are added.

The mixture is stirred at ambient temperature for 2 hours, poured into water, extracted with methylene chloride, washed with sodium bicarbonate, dried and then evaporated. The residue is recrystallized in a mixture of diisopropyl oxide and ethyl acetate. 3.7 g of the expected product are obtained. Yield—84%. Melting point: 189°–190° C.

## EXAMPLE 6

6-[p-(1-adamantylthio)phenyl]-2-naphthoic acid.

Compound of Formula II wherein $R'_2$=H, $R'_6$=OH and $R'_3$=1-adamantylthio

3 g (7 mmol) of the ester obtained in Example 5(b) are treated with a solution of soda in methanol (150 ml, 5N). The reaction mixture is heated at reflux for 12 hours, evaporated, taken up in water and acidified with concentrated HCl. The resulting solid is filtered and dried under a vacuum on phosphoric anhydride. The resulting white solid is pulverized in methanol at reflux, cooled and filtered. 2.5 g of the expected product are thus obtained. Yield—86%. Melting point: 334°–336° C.

## EXAMPLE 7

Methyl ester of 6-(3,4-dimethoxy phenyl)-2-naphthoic acid. Compound of Formula II wherein $R'_2$=$R'_3$=$R'_6$=—$OCH_3$.

0.93 g (38.3 mAtg) of magnesium in 20 ml of THF are slowly treated with 5.5 g (25.5 mmol) of 4-bromoveratrole. At the end of the addition, the mixture is heated at reflux for two hours, and then cooled. At this point 3.48 g (25.5 mmol) of anhydrous $ZnCl_2$ are added and the mixture is stirred one hour at ambient temperature. 3.98 g (15 mmol) of methyl 6-bromo-2-naphthoate are then added followed by the addition of 130 mg of $NiCl_2$/DPPE complex. The mixture is stirred for two hours a ambient temperature and then poured into water and extracted with dichloromethane. The organic phase is dried and evaporated. The residue is recrystallized in a mixture of isopropyl ether and ethyl acetate. 3.4 g of the expected product are obtained. Yield—70%. Melting point: 147°–148° C.

## EXAMPLE 8

6-(3,4-dimethoxyphenyl-2-naphthoic acid. Compound of Formula II wherein $R'_2$=$R'_3$=—$CCH_3$ and $R'_6$=OH

2.6 g (8 mmol) of the ester obtained in example 7 are treated with a solution of soda in methanol (200 ml, 2N). The reaction mixture is heated at reflux for 8 hours, evaporated, taken up in water, acidified with concentrated HCl, and filtered. The solid thus obtained is dried under a vacuum (on $P_2O_5$). The resulting white solid is pulverized in methanol at reflux, cooled and then fil-

tered. 2.3 g of the expected product are obtained. Yield—92%. Melting point: 241°-243° C.

## EXAMPLE 9

Methyl ester of 6-[3-(1-adamantyl)-4 methoxy phenyl]-2-naphthoic acid. Compound of Formula II wherein $R'_3$—$OCH_3$, $R'_2$=1-adamantyl and $R'_6$=$OCH_3$

(a) 2-(1-adamantyl)-4-bromophenol.

34.6 g (200 mmol) of p-bromophenol and 30.4 g (200 mmol) of 1-adamantanol are dissolved in 100 ml of dichloromethane. To the resulting solution there are slowly added 10 ml of concentrated sulfuric acid. The mixture is stirred for 8 hours at ambient temperature, poured into water, neutralized with sodium bicarbonate, extracted with methylene chloride, dried and evaporated. After recrystallization in isooctane 52.8 g of the expected product are obtained. Yield—86%. Melting point: 140°-141° C.

(b) 2-(1-adamantyl)-4-bromoanisole.

To a suspension of sodium hydride (80% in oil, 4.32 g, 144 mmol) in 50 ml of THF, there are slowly added, while maintaining the temperature at 20° C., 36.8 g (120 mmol) of 2-(1-adamantyl)-4-bromophenol. The mixture is stirred for 1 hour at ambient temperature at which point 9 ml (144 mmol) of methyl iodide are added. The mixture is then stirred for 2 hours at 20° C. poured into water, extracted with ether, dried and evaporated. The product is purified by passage through a silica column (10 × 30 cm), eluting with a mixture of hexane (90%) and dichloromethane (10%). On evaporation, 26.2 g of a white solid are obtained. Yield—68%. Melting point: 138°-139° C.

(c) Methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid.

To a suspension of magnesium (1.64 g, 67.5 m Atg) in 30 ml of THF, there is added a solution of 1.4 g (4.5 mmol) of 2-(1-adamantyl)-4-bromoanisole and 0.39 ml of dibromoethane in 10 ml of THF. The mixture is stirred until the reaction is initiated and then there is slowly added a solution of 13.1 g (40.8 mmol) of 2-(1-adamantyl)-4-bromoanisole in 90 ml of THF. The mixture is heated at reflux for 2 hours, and then cooled to 20° C. There are then added 6.2 g (45 mmol) of anhydrous $ZnCl_2$. The mixture is stirred for 1 hour at 20° C. at which point 7.95 g (30 mmol) of methyl 6-bromo-2-naphthoate are added followed by the addition of 300 g of $NiCl_2$/DPPE complex. The mixture is stirred again for 2 hours at 20° C., poured into water, extracted with $CH_2Cl_2$, dried and evaporated. The product is isolated by column chromatography, eluting with a mixture of heptane (70%) and dichloromethane (30%) and then recrystallized in ethyl acetate. 12.2 9 of the expected product are obtained. Yield—78%. Melting point: 222°-223° C.

## EXAMPLE 10

6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid. Compound of Formula II wherein $R'_3$=$OCH_3$, $R'_2$=1-adamantyl and $R'_6$=OH.

10.5 g of the ester obtained in Example 9(c) are treated with a solution of soda in methanol (200 ml, 4.2 N). The mixture is heated at reflux for 48 hours. The solvents are evaporated and the resulting residue is taken up in water and acidified with concentrated HCl. The solid is filtered and dried under a vacuum over phosphoric anhydride.

The resulting white solid is recrystallized in a mixture of THF and ethyl acetate. 8.2. g of the expected product are obtained. Yield—81%. Melting point: 325°-327° C.

## EXAMPLE 11

Methyl ester of 6-[3-(1-adamantyl)-4-tert.butyl dimethylsilyloxylphenyl]-2-naphthoic acid. Compound of Formula I wherein $R_4$=$R_5$=H, $R_2$=1-adamantyl, $R_3$=$OSi(CH_3)_2C_3H_7$ and

$R_3$ = $OSi(CH_3)_2C_3H_7$ and $R_1$ = $-\overset{O}{\overset{\|}{C}}OCH_3$

(a) 2-(adamantyl)-4-bromo-1-tert.butyldimethylsilyloxybenzene.

30.7 g of 2-adamantyl-4-bromophenol (100 mmol) are dissolved in DMF (200 ml). There are then added triethylamine (15.4 ml, 110 mmol) and 4-N,N-dimethylaminopyridine (DMAP, 500 mg,4 mmol).

To the resulting solution there is slowly added a solution of tert.butyldimethylsilyl chloride (15.7 g, 104 mmol) in DMF (100 ml). The mixture is stirred at ambient temperature for 4 hours, poured into water, extracted with ether, dried ($MgSO_4$) and evaporated. The residue is dissolved in hexane and purified by passage through a silica column (eluant: hexane). 36.2 g (86%) of 2-adamantyl-4-bromo-1-tert.butyldimethylsilyloxybenzene are obtained. Melting point: 111° C.

(b) Methyl ester of 6-[3-(1-adamantyl)-4-tert.butyldimethylsiloxyphenyl]-2-naphthoic acid.

33.3 g (79 mmol) of the compound produced in part (a) above, dissolved in 200 ml of THF are slowly added to a suspension of magnesium (2.9 g, 118 Atg) in 60 ml of THF. Once the addition is complete, the mixture is heated at reflux for 2 hours at which point the temperature of the mixture is permitted to return to ambient temperature. 10.8 g (79 mmol) of anhydrous zinc chloride are added and the mixture is stirred for one hour at ambient temperature, at which point 10.5 g (39.5 mmol) of methyl 6-bromo-2-naphthoate and 500 mg of $NiCl_2$/DPPE complex are added. This mixture is then stirred for 2 hours at ambient temperature, poured into water, extracted with $CH_2Cl_2$, dried and evaporated. The residue is chromatographed on a silica column (eluant: mixture of heptane (70%) and ether (30%). 18.5 (90%) of the methyl ester of 6-[3-(1-adamantyl)-4 TM tert.butyldimethylsilyloxyphenyl]-2-naphthoic acid are obtained. Melting point: 152°-153° C.

## EXAMPLE 12

Methyl ester of 6[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid. Compound of Formula I wherein $R_4$=$R_5$=H, $R_2$=1-adamantyl, $R_3$=OH and $R_1$=$COOCH_3$

17.5 g (33 mmol) of the ester produced in Example 11 are dissolved in 300 ml of THF. To this solution there is added 36.6 ml of a molar solution of tetrabutylammonium fluoride in THF. The mixture is stirred for 2 hours at ambient temperature, poured into water and extracted with $CH_2Cl_2$. The organic phase is recovered, dried ($MgSO_4$), and the solvents evaporated. The resulting residue is recrystallized in a mixture of ethylacetate (70%) and THF (30%) to give the expected ester. 11 g (81%). Melting point: 266° C.

## EXAMPLE 13

6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid. Compound of Formula I wherein $R_4=R_5=H$, $R_2$= 1-adamantyl, $R_3$=OH and $R_1$=COOH.

5 g (12 mmol) of the ester obtained in Example 12 are treated with 200 ml of methanolic soda (2N), under nitrogen, for 8 hours. The solvents are evaporated and the residue taken up in water and acidified to pH 1 (concentrated HCl). The reaction mixture is filtered, washed with water, the solid product is extracted with ethyl ether, dried ($MgSO_4$) and evaporated. The residue is recrystallized in isopropylether, yielding 3.8 g (79%) of the expected acid. Melting point: 270°-271° C.

## EXAMPLE 14

Methyl ester of 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein $R_4=R_5=H$, $R_2$= 1-adamantyl, $R_3$=—$OC_{10}H_{21}$ and $R_1$=$COOCH_3$

(a) 2-(1-adamantyl)-4-bromo-1-decyloxy benzene.

To a suspension of sodium hydride (80% in oil, 3.2 g, 104 mmol) in 100 ml of THF, there is slowly added a solution of 2-(1-adamantyl)-4-bromophenol (29 g, 95 mmol) in 200 ml of THF. The mixture is stirred until the evolution of gas ceases at which point 27.8 g (23 ml, 104 mmol) of 1-iododecane and 100 ml of DMF are added. The mixture is stirred for 12 hours at ambient temperature, poured into water, extracted with ether, dried and the solvents evaporated. The resulting residue is purified by passage through a silica column (eluant: heptane), yielding 40.7 g (96%) of 2-(1-adamantyl)-4-bromo-1-decyloxybenzene. Melting point: 69°-70° C.

(b) Methyl ester of 6-[3-(1-adamantyl) TM 4-decyloxyphenyl]-2-naphthoic acid.

In a manner analogous to Example 9c, starting with 17.9 g (40 mmol) of the brominated derivative obtained in part (a) above, and 5.3 g of methyl 6-bromo-2-naphthoate, 7.4 g (67%) of the expected ester are obtained. Melting point: 113°-114° C.

## EXAMPLE 15

6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid. Compound of Formula I wherein $R_4=R_5=H$, $R_2$= 1-adamantyl, $R_3$=—$OC_{10}H_{21}$ and $R_1$=COOH

6.3 g (11 mmol) of the ester obtained in Example 14 dissolved in 200 ml of THF are treated at reflux with 200 ml of 2M methanolic soda for 4 hours. The solvents are evaporated and the residue is taken up in water, acidified to pH 1 (concentrated HCl), filtered, washed with water and the solid is extracted with ether. The extract is dried and the solvent evaporated. The resulting residue is treated with 700 ml of ethyl acetate at reflux. On cooling 5.9 g (97%) of the expected acid are obtained. Melting point: 214°-215° C.

## EXAMPLE 16

Methyl ester of 6-[3-(1-adamantyl)-4-hexyloxy-phenyl]-2-naphthoic acid. Compound of Formula I wherein $R_4=R_5=H$, $R_2$= 1-adamantyl, $R_3$=—$OC_6H_{13}$ and $R_1$=—$COOCH_3$

5.3 g (13 mmol) of the ester obtained in Example 12 are dissolved in 100 ml of DMF and added to a suspension of NaH (80% in oil; 0.46 g; 15.4 mmol) in DMF (50 ml). The mixture is stirred at ambient temperature until the evolution of gas ceases, at which point 1-iodohexane (3.26 g; 2.3 ml; 15.4 mmol) is added. This mixture is then stirred for 4 hours at ambient temperature, poured into water, extracted with ether, dried and evaporated. The residue is purified by passage through a silica column (eluant: mixture of dichloromethane—50% and hexane—50%), then recrystallized in isooctane to give 5.5 g (87) of the expected pure product. Melting point: 129°-130° C.

## EXAMPLE 17

6-[3-(1-adamantyl)-4-hexyloxypheryl]-2-naphthoic acid. Compound of Formula I wherein $R_4=R_5=H$, $R_2$= 1-adamantyl, $R_3$=—$OC_6H_{13}$ and $R_1$=—COOH

In a manner analogous to Example 15, starting with 4.2 g (8.4 mmol) of the ester obtained in Example 16, 3.8 g (95%) of 6-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid are obtained. Melting point: 260°-261° C.

## EXAMPLE 18

Methyl ester of 6-[3-(1-adamantyl)-4-methoxy phenyl]-4-acetoxy-1-methyl-2-naphthoic acid. Compound of Formula I wherein $R_4=CH_3$, $R_5$=—$OCOCH_3$, $R_2$= 1-adamantyl, $R_3$=—$OCH_3$ and $R_1$=—$COOCH_3$

47.6 g (148 mmol) of 2-(1-adamantyl)-4-bromoanisole and 13.9 g (6.3 ml, 74 mmol) of dibromoethane, dissolved in 100 ml of THF are added slowly to a suspension of magnesium (5.4 g, 222 mmol) in the THF (1000 ml). The mixture is brought to reflux for 2 hours at which point zinc chloride (20.2 g, 148 mmol) is added. The mixture is stirred for 1 hour and there are successively added 24.9 g (74 mmol) of methyl 4-acetoxy-6-bromo-1-methyl-2-naphthoate and 500 mg of $NiCl_2DPPE$ complex. This mixture is stirred for 8 hours at ambient temperature, poured into a saturated aqueous solution of ammonium chloride, extracted with $CH_2Cl_2$, dried and the solvents evaporated. The resulting residue is purified by passage through a silica column (eluant: mixture of hexane, 40%, and $CH_2Cl_2$, 60%). The resulting product is recrystallized in isopropyl ether, yielding 23.5 g (64%) of the expected ester. Melting point: 201°-202° C.

## EXAMPLE 19

6-[3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid. Compound of Formula I wherein $R_4=CH_3$, $R_5$=OH, $R_2$= 1-adamantyl, $R_3$=$OCH_3$ and $R_1$=COOH

23 g (46 mmol) of the ester obtained in Example 18 are treated at reflux for12 hours with 300 ml of methanolic soda (2N). The solvents are evaporated and the residue is taken up in water and acidified to pH 1 (concentrated HCl). The solid is filtered, washed with water, dissolved in ethyl ether, dried ($MgSO_4$) and evaporated. The resulting residue is recrystallized in ethyl acetate to give 18.7 g (92%) of the expected acid. Melting point: 281°-283° C.

EXAMPLE 20

Methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-hydroxy-1-methyl-2-naphthoic acid. Compound of Formula I wherein $R_4=CH_3$, $R_5=OH$, $R_2=$1-adamantyl, $R_3=OCH3$ and $R_1=COOCH_3$

17 g (38 mmol) of the acid obtained in Example 19 are treated for 12 hours at reflux with 200 ml of methanol containing 2 ml of sulfuric acid. The solvents are evaporated and the residue is taken up in water, extracted with ether, dried and evaporated. The residue is purified by passage through a silica column using as the eluant a 90:10 mixture of ether/THF. The product is recrystallized in ethyl acetate to obtain the expected pure ester —15 g (86%). Melting point: 272°–274° C.

EXAMPLE 21

Methyl ester of 6-[3-(1-adamantyl)-4-methoxy-phenyl]-1-methyl-2-naphthoic acid. Compound of Formula I wherein $R_4=CH_3$, $R_5=H$, $R_2=$1-adamantyl, $R_3=OCH_3$ and $R_1=$—$COOCH_3$

(a) Methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-dimethylaminothiocarbonyloxy-1-methyl-2-naphthoate.

4.56 g of the ester obtained in Example 20, dissolved in THF (100 ml) are slowly added to a suspension of sodium hydride (80% in oil, 360 mg, 12 mmol) in DMF (50 ml). The mixture is stirred for 1 hour at ambient temperature and then for 1 hour at 40° C. There are then added 1.75 g (14 mmol) of dimethylthiocarbamoyl chloride, and the mixture is stirred initially at ambient temperature for 2 hours and then at 40° C. for 2 hours. The reaction mixture is poured into water, extracted with ether, dried, and the solvents evaporated. The product is purified by passage through a silica column (eluant: $CH_2Cl_2$), yielding 4 g (74%) of the expected intermediate product. Melting point: 137°–138° C.

(b) Methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-4-dimethylcarbonythio-1-methyl-2-naphthoate.

3.8 g (7 mmol) of the ester obtained above in part (a) are heated under nitrogen at 260° C. for 0.5 hour. The residue is taken up in methylene chloride and purified by passage through a silica column (eluant: $CH_2Cl_2$). The resulting gum is taken up in isopropyl ether, yielding 3.3 g (87%) of the desired intermediate. Melting point: 201°–202° C.

(c) Methyl ester of 6-[3-(1-adamantyl)-4.methoxyphenyl]-1-methyl-2-naphthoic acid.

The intermediate obtained above in part b) - (11 g, 20 mmol) is dissolved in 500 ml of ethanol. 20 g of Raney nickel are added and the reaction mixture is heated at reflux for 4 hours. 20 g of nickel are then added and the mixture is heated again for 1 hour, at which point the mixture is cooled, concentrated and taken up in $CH_2Cl_2$ (1000 ml). The precipitate is filtered and the filtrate is recovered, dried and evaporated. The product is purified by passage through a silica column (eluant: $CH_2Cl_2$) and recrystallized in a mixture of ethyl acetate (90%) and THF (10%), yielding 8 g (90%) of the methyl ester of 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid. Melting point: 238°–239° C.

EXAMPLE 22

6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid. Compound of Formula I wherein $R_4=CH_3$, $R_5=H$, $R_2=$1-adamantyl, $R_3=OCH3$ and $R_1=COOH$.

6.8 g (15.4 mmol) of the ester obtained in Example 21(c) are treated as in Example 10 to give 5.8 g (88%) of the corresponding acid. Melting point: 300°–302° C.

EXAMPLE 23

6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthalene methanol. Compound of Formula I wherein $R_4=R_5=H$, $R_2=$1-adamantyl, $R_3=OCH_3$ and $R_1=$—$CH_2OH$

1.3 g (3 mmol) of the ester obtained in Example 9 dissolved in THF (5 ml) are treated with 171 mg (4.5 mmol) of $LiAlH_4$. The mixture is heated at reflux, cooled and treated with a saturated aqueous solution of the double tartrate of sodium and potassium. The reaction mixture is filtered, evaporated to dryness, and the residue is recrystallized in cyclohexane, yielding 1.0 g (83%) of the 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthalene methanol. Melting point: 163°–164° C.

EXAMPLE 24

Ethylamide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Compound of Formula I wherein $R_4=R_5=H$, $R_2=$1-adamantyl, $R_3=OCH_3$ and $R_1=$—$CONHC_2H_5$.

(a) 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid chloride.

4.75 g (1.15 mmol) of the acid obtained in Example 10 in 200 ml of dichloromethane are treated with 2.08 g (2.3 ml, 1.15 mmol) of dicyclohexamine. The mixture is stirred at ambient temperature until dissolution. The solvents are evaporated and the residue taken up in ether. The solid thus formed is filtered (6.8 g) and then taken up in methylene chloride (50 ml). 1.37 g (0.84 ml, 1.15 mmol) of thionyl chloride are added. The salt formed is filtered and the filtrate is recovered, evaporated and dried. The resulting solid (3.9 g) is used as such in the following step.

(b) Ethylamide of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid.

1.3 g (3 mmol) of the acid chloride produced in (a) above are dissolved in 20 ml of THF. 405 mg (600 µl, 9 mmol) of ethylamine are added and the mixture is stirred for 2 hours at ambient temperature. The mixture is then poured into water, extracted with $CH_2Cl_2$, dried and evaporated. The residue is recrystallized in ethyl acetate, yielding 1.1 g (85%) of the expected ethylamide. Melting point: 220°–221° C.

EXAMPLE 25

Morpholide of 6-[3-(1-adamantyl]-4-methoxyphenyl]-2-naphthoic acid.

In a manner analogous to Example 24, starting with 1.3 g of acid chloride produced in part (a) of Example 24 and 780 mg (780 ml, 9 mmol) of morpholine, there are obtained 1.3 g (91%) of the expected morpholide. Melting point: 212°–213° C.

## EXAMPLE 26

Methyl ester of 6-[3-tert.butyl-4-methoxy phenyl]-2-naphthoic acid. Compound of Formula II wherein $R'_2$=tert.butyl, $R'_3=R'_6=OCH_3$.

(a) 4-bromo-2-tert.butyl anisole.

3.10 g (22.6 mmol) of aluminum chloride are added all at once to a mixture of 63.5 g (339 mmol) of p-bromoanisole and 31.4 g (330 mmol) of tert.butyl chloride. The mixture is stirred at ambient temperature until the evolution of gas ceases (about 15 minutes). The mixture is then heated at 80° C. for 15 minutes and poured into ice. 300 ml of water are added and the mixture is extracted with ether.

The organic phase is dried ($MgSO_4$), the solvents evaporated and the residue purified by chromatography on a silica column (eluant: mixture of methylene chloride—10% and hexane—90%). After evaporation of the solvents, 4-bromo-2-tert.butyl anisole under the form of a colorless oil which crystallized on cooling is obtained. 31.9 g (39%).

(b) Methyl ester of 6-[3-tert.butyl-4-methoxy phenyl]-2-naphthoic acid.

There is slowly added, drop by drop, a solution of 18.8 g (77 mmol) of 4-bromo-2-tert.butyl anisole to 2.26 g (93 mmol) of magnesium turnings and a crystal of iodine. The mixture is heated until the Grignard begins to form, at which point the remainder of the solution containing the brominated derivative is poured in a manner to maintain a regular reflux. Once the addition is complete, the mixture is heated at 40° C. for 30 minutes, diluted with 200 ml of THF and cooled to ambient temperature. 12.7 g (93 mmol) of dry zinc chloride in solution in 20 ml of THF are added and the mixture is stirred for 30 minutes at ambient temperature. There are then successively added 12.1 g (46 mmol) of methyl 6-bromo-2-naphthoate and 300 mg of $NiCl_2$/DPPE complex.

The mixture is stirred for 10 hours at ambient temperature. 300 ml of water are added and the THF is evaporated. The remainder is extracted with methylene chloride. The organic phase is dried ($MgSO_4$), filtered, evaporated and purified by passage through a silica column (eluant: mixture of 50% dichloromethane and 50% hexane). After evaporation of the solvents, the resulting residue is recrystallized in hexane to give the expected ester: 11.5 g (72%). Melting point—160° C.

## EXAMPLE 27

6-(3-tert.butyl-4-methoxyphenyl)-2-naphthoic acid. Compound of Formula II wherein $R'_2$=tert.butyl, $R'_3=OCH_3$ and $R'_6=OH$.

In a manner analogous to Example 15, starting with 7.0 g (20 mmol of the ester obtained in

Example 26, 6.0 g (90%) of the expected acid are obtained. Melting point: 268° C.

## EXAMPLE 28

Methyl ester of 6-[3-(1,1-dimethyldecyl)-4-methoxy-phenyl]-2-naphthoic acid. Compound of Formula I wherein $R_4=R_5=H$, $R_2=C(CH_3)_2C_9H_{19}$, $R_3=OCH_3$ and $R_1=—COOCH_3$

A solution of 16 g (45 mmol) of 2-(1,1-dimethyldecyl)-4-bromo anisole in 60 ml of THF is slowly added to of magnesium and a crystal of iodine. The mixture is slightly heated at the beginning of the addition until the reaction of formation of the Grignard is initiated. Then the remainder of the solution containing the brominated derivative is added in a manner to maintain a regular reflux. Once the addition is complete, the mixture is stirred for 30 minutes at 50° C. and then cooled to ambient temperature. 7.4 g (54 mmol) of zinc chloride in solution in 50 ml of THF are added. The mixture is stirred for 30 minutes at ambient temperature, 6.6 g (25 mmol) of methyl 6-bromo-2-naphthoate are added and then 175 mg of $NiCl_2$/DPPE complex. The mixture is stirred for 3 hours at ambient temperature at which point 250 ml of water are added. The THF is evaporated under reduced pressure and the residue is extracted with dichloromethane, dried and the solvent evaporated. The residue is purified by passage through a silica column (eluant: mixture of 60% dichloromethane and 40% hexane). On evaporation, a solid is obtained which is recrystallized twice in hexane to give the methyl ester of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid: 7.05 g (61%). Melting point: 92° C.

## EXAMPLE 29

6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl)-2-naphthoic acid. Compound of Formula I wherein $R_4=R_5$=H, $R_2=C(CH_3)_2C_9H_{19}$, $R_3=OCH_3$ and $R_1$=COOH.

In a manner analogous to Example 15, starting with 3.6 g of the ester obtained in Example 28, 3 g (87%) of 6-[3-(1,1-dimethyldecyl)-4-methoxyphenyl]-2-naphthoic acid are obtained. Melting point: 180° C.

## EXAMPLES OF COMPOSITIONS

Example A—Fatty Cream Wherein The Active Principle is in Suspension

| | |
|---|---|
| 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid | 0.001 g |
| A combination of nonionic E/H emulsifiers and a fatty body of mineral origin sold by Goldschmidt under the trade name "Protegin X" | 25.00 g |
| Petrolatum oil | 10.00 g |
| Preservatives, sufficient amount | |
| Water, sufficient amount for | 100.00 g |

In that example, the active compound can be replaced by the same amount of 6-[3-(1-adamantyl)-4-methoxy phenyl]-1-methyl 2-2-naphthoic acid.

Example B—Skin Cream—A fluid Cream Wherein The Active Principle is in Suspension

| | |
|---|---|
| Methyl ester of 6(4-tert.butyl phenyl)-2-naphthoic acid | 0.02 g |
| Sorbitan stearate polyoxyethylenated with 20 moles of ethylene oxide sold by Atlas under the trade name "Tween 60" | 5.00 g |
| Sorbitan monostearate sold by Atlas under the trade name "Span 60" | 2.00 g |
| Cetyl alcohol | 5.00 g |
| Triglycerides of capric and caprylic acids sold by Dynamit Nobel under the trade name "Miglyol 812" | 10.00 g |
| Preservatives, sufficient amount | |
| Water, sufficient amount for | 100.00 g |

Example C—Gel For The Skin or Scalp Wherein The Active Principle is in Suspension.

| | |
|---|---|
| Methyl ester of 6-(4-t.butyl phenyl)-2-naphthoic acid | 0.10 g |
| Ethanol | 20.00 g |
| Hydroxypropyl cellulose, sold by Hercules under the trade name "Klucel HF" | 2.00 g |
| Preservative, sufficient amount | |
| Water, sufficient amount for | 100.00 g |

Example D—Lotion of the Skin

| | |
|---|---|
| 6-[3-(1-adamantyl)-4-methoxyphenyl]-1-methyl-2-naphthoic acid | 0.1 g |
| Polyethylene glycol 400 | 70.0 g |
| Ethanol | 29.9 g |

In that example, the active compound can be replaced by the same amount of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid.

Example E—Unguent For The Skin

| | |
|---|---|
| 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid | 0.001 g |
| Lanolin | 50 g |
| Vaseline, sufficient amount for | 100 g |

Example F—Oral Composition—0.30 g gelule.

| | |
|---|---|
| 6-[3-(1-adamantyl)-4-methoxy phenyl]-2-naphthoic acid | 0.003 g |
| Cornstarch | 0.060 g |
| Lactose, sufficient amount for | 0.300 g |

The resulting powder is packaged in a gelule whose wall is made of gelatin, $TiO_2$ and a preservative.

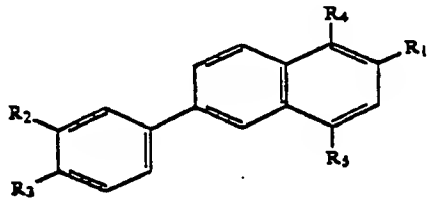
Example G—Capsule Containing 0.400 g Of The Following Suspension

| | |
|---|---|
| Ethylamide of 6-[3-(1-adamantyl)-4-methoxy-phenyl]-2-naphthoic acid | 0.005 g |
| Glycerine | 0.200 g |
| Sucrose | 0.050 g |
| Polyethylene glycol 400 | 0.050 g |
| Purified water, sufficient amount for | 0.400 g |

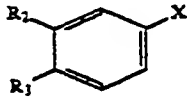
This suspension is packaged in a capsule made of gelatin, glycerine titanium dioxide and water.

What is claimed is:

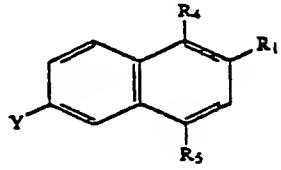
1. A process for preparing a compound having the formula



comprising coupling, in an anhydrous solvent and in the presence of, as a reaction catalyst, a transition metal or a complex thereof, a magnesium, lithium or zinc derivative of a compound of the formula



with a halogenated naphthalene compound of the formula



wherein

$R_1$ represents (i)

or (ii) $—CH_2OH$,

$R_6$ represents

or $OR_7$ wherein $R_7$ represents hydrogen, alkyl having 1–20 carbon atoms, monohydroxyalkyl or polyhydroxyalkyl, r' and R" represent hydrogen, lower alkyl, mono or polyhydroxyalkyl, aryl or a residue of an amino acid or an amino sugar selected from the group consisting of glucosamine, galactosamine and mannosamine, or together form a heterocycle selected from the group consisting of piperidino, piperazino, morpholino and pyrrolidino,

$R_2$ represents hydrogen, branched or straight chain alkyl having 1–15 carbon atoms, alkoxy having 1–4 carbon atoms or a cycloaliphatic radical,

$R_3$ represents hydrogen, hydroxy, branched or straight chain alkyl having 1–4 carbon atoms, alkoxy having 1–10 carbon atoms, a cycloaliphatic radical selected from the group consisting of 1-methyl cyclohexyl and 1-adamantyl, a thiocycloaliphatic radical, or $—O—Si(CH_3)_2—R_8$ wherein $R_8$ represents linear or branched lower alkyl,

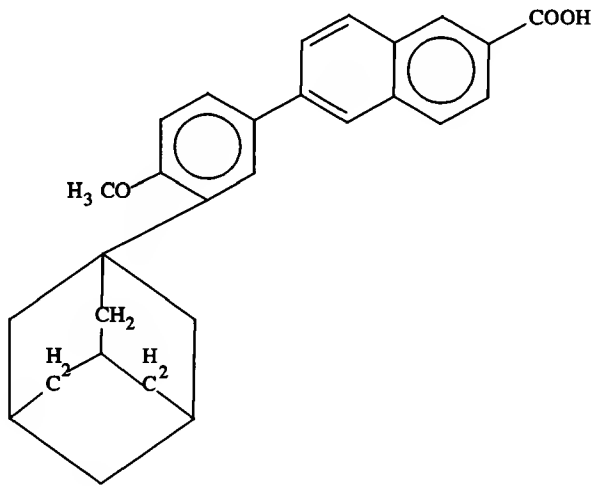
$R_4$ and $R_5$, each independently, represent hydrogen, lower alkyl, hydroxy or lower acyloxy, and

X and Y represent Cl, Br, F or I.

2. The process of claim 1 carried out at a temperature ranging from −20° to +30° C.

* * * * *

# APPENDIX B




## Adapalene